

An Audio Music Self-management to Improve ART Adherence in Rural Georgia
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Marcia M. Holstad, Ighovwerha Ofotokun, Eugene Farber, Melinda Higgins, Drenna Waldrop-Valverde

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Background

a. Specific Aims:

The project has three primary aims and two exploratory aims.

1.0 Revise and adapt the Live Network (LN) program and manual for rural persons living with HIV/AIDS (PLWHA) and develop into a mobile application.

2.0 Conduct a randomized controlled trial to test the efficacy of the program. When compared with an educational music control condition at 3, 6, and 9 months post-baseline, those randomized to the LN will have:

H1: Significantly higher mean antiretroviral therapy (ART) adherence rates (measured by pill counts, self report).

H2: Significantly higher mean levels of ART drug levels in hair sample analyses.

H3: Significantly better clinical indicators: higher mean CD4 lymphocyte counts and percents, a larger proportion achieving virologic suppression (proportion with HIV RNA PCR <50 copies/ml), and smaller proportion with evidence of drug resistance, all as measured by medical record review.

3.0 Explore: a) the effects of LN on symptoms and symptom management; b) the roles of self-efficacy, outcome expectancies, and personal goal setting as mediators, and depression and health literacy as moderators of adherence

4.0 Evaluate the acceptance and adoption of the LN and educational program (EP) mobile application software (app) by examining: a) the antecedent influences of performance expectancy, effort expectancy and hedonic motivation on the behavioral intent-to-use and usage (frequency and duration) of the LN and EP mobile apps; and b) the moderating effects of electronic health (eHealth) literacy and smartphone experience on behavioral intent and subsequent LN/EP mobile app usage.

H1: Performance expectancy, effort expectancy, and hedonic motivation have direct, positive associations with behavioral intent to use the LN/EP mobile apps.

H2: Behavioral intent has a direct positive association with both the frequency and the duration of the LN/EP mobile app use.

H3: eHealth literacy and smartphone experience moderate the association between behavioral intent antecedents (performance expectancy, effort expectancy, and hedonic motivation) and behavioral intent. Low eHealth literacy and smartphone inexperience will weaken the association between the antecedents and behavioral intent.

5.0 Explore: a) associations of baseline antiretroviral treatment (ART) adherence with characteristics such as demographics, self-reported behaviors and symptoms, health literacy, access to care, disease progression, comorbidities, and substance use in a randomized interventional study of HIV and mobile application technology in rural Georgia.

H1: Participants changing ART medication regimen or those that have developed new resistance are different than those starting ART.

b. Preliminary Studies

This project effectively builds on the NIH/NINR funded pilot study (R21 NR010862) in which we developed and tested the LN in a large urban HIV clinic that serves primarily low income, African American clients diagnosed with AIDS. Prior to developing the LN songs, we conducted a music preference survey of 135 patients from the Grady Health System Infectious Disease Program, the site for the urban pilot project, who had been on ART for at least 6 months. This survey posed questions about music genre preferences, a ranking of top preferences, whether they own an MP3 player, demographics, and prescribed ART. 76% of the participants were between 40-59 years old, 86% were African American, and 59% owned an MP3 or personal CD player. The top 10 genres used to develop the LN are in order: Gospel, Rhythm and Blues (R&B), Oldies, Hip-hop, Motown, Smooth Jazz, Easy Listening, Soul, Blues, and House.

We then developed the LN program and manual and conducted 3 focus groups to assess its utility, appeal, and feasibility. Participants included 10 men and 8 women who had been on ART for at least 6 months. All were given an MP3 player with the program to listen to and manual to read for two weeks prior to the focus group. The average age was 45 years; 83% were African American and 2% were Hispanic. Eleven self identified as heterosexual, 4 homosexual, 3 bisexual; 61% reported earning from 0 to \$1000 per month. Participants completed an evaluation questionnaire about the program, manual, and study 800-number. Utility: The primary benefits of the program were improved knowledge both for themselves and families and friends and motivational messages that spurred self-management activities, including adherence. They felt empowered to set goals, seek reliable health information, as well as enabled to embrace life and improve self-image. The upbeat songs helped raise their mood, provided hope, and encouraged perseverance. Appeal: Music served as the “hook” that engaged listeners to listen to the lyrics. “Good” songs were described as ‘encouraging’ and ‘uplifting.’ Talk show segments were well received, but playback value was less than the songs. Feasibility: The MP3 player delivery was easy to use, the organization of the program (talk show + music and music only) was appreciated, and the manual was informative, though deemed too long. None of the participants expressed concern that listening to the program or reading the manual in public would expose their HIV status. A few improvements were suggested, including modifying “depressing” song lyrics. For instance, the opening lyrics in one song, It Ain’t Easy (a song meant to validate the day-to-day struggles of people living with HIV/AIDS), were specifically mentioned as out-of-character with the LN’s positive approach. Other suggestions were to include more songs and different caller scenarios and shorten the 175 page manual. A few wanted a means to discuss content or questions. This manuscript is in review in Music and Medicine.

We conducted a pilot RCT at the same site to compare the program with usual care (at least 2 visits with a Nurse Educator). We enrolled 77 persons who started or changed ART within the previous 6 months. Participants were randomized 2:1 to LN (n = 51) or standard care (n =26) and completed baseline (T1), 6 week (T2), and 12 week (T3) assessments and monthly pill counts (PC). Blood draws measured plasma antiretroviral medication trough levels at 12 weeks, an innovative measure of adherence. Significance for this small sample pilot was set at $p \leq .1$. Mean age was 44.7 yrs; 65% were male; 88% were African American; participants were HIV-infected for 9.6 years (median). Median monthly income was \$674. At T3 we found adherence declined over time for both groups; however the drop was greater for the control group compared to the LN group: 67% (14 of 21) of controls but only 52% (22 of 42) of intervention subjects dropped below baseline values (NS). While not statistically significant, PCs at T3 were higher for intervention participants (77.8% vs.70.6%). Also at T3, 80.5% of LN subjects vs. 72.7% of controls had antiretroviral plasma trough levels at or above therapeutic range (n=63, NS). CD4 and viral load (VL) were analyzed using multilevel mixed models. There was a larger proportion of LN group with undetectable VL log (≤ 1.88) at all time points. VL log (inverse transformed) yielded a significant group by time interaction ($t=1.890$, $p=0.067$, and model deviance change chi-square=3.07, $df=1$, $p=0.08$) for the LN. No significant differences were seen for CD4. Adherence self-efficacy scores improved in the LN group from T1 to T3 (chi-square=5.1, $df=2$, $p=0.080$). No significant changes were seen for the control group (chi-square=2.6 ($df=2$), $p=0.273$). Wilcoxon pairwise post hoc tests using Bonferroni corrected $\alpha=0.033$ indicated significant differences between T1 and T3 ($Z=-2.39$, $p=0.017$) and between T2 and T3 ($Z=-2.39$, $p=0.017$). Self-efficacy had the largest effect sizes seen in this study; the largest changes occurred between T1 and T3 indicating that the study should be run longer to establish sustainable improvements. For the LN group, ART self-efficacy scores increased by 6.05 ($sd=12.97$) for an estimated effect size of 0.47, a medium effect size. Participants with higher CES-D scores (depressive symptoms) at T1 were 1.08 times more likely ($p=0.03$) to have drug trough levels below the therapeutic range at T3. There were no differences between or within groups in numbers of symptoms or symptom distress. Small sample size and short duration of follow-up limit our results. All

measures of adherence were subject to bias: patients can dump pills prior to PC, as well as “load” medications prior to blood level testing. We feel these are encouraging trends in adherence, VL, and self-efficacy. Measuring adherence using therapeutic drug levels was innovative, easy to collect, and enhanced the objectivity of the findings. These results were presented at the Association of Nurses in AIDS Care annual meeting in November, 2010. LN program evaluation: LN participants completed an evaluation rating satisfaction, likability, usage, and suggestions for improvement at the end of the study. 47 of 51 LN participants completed the evaluation and expressed overwhelmingly positive responses to the questions. The following are the percentage of persons who agreed or strongly agreed with the items: 87% liked the DJ segments, 83% liked the music styles, and 87% reported the lyrics were easy to understand. For the manual, 91.5% felt it was easy to use, 89.6% felt it was understandable, and 89.1% liked it and felt it was helpful. On a scale from ‘none’ to ‘greater than 10 times’, 17% reported listening to the songs 5 to 10 times and 42% reported listening >10 times in the prior 3 months. 42% reported listening to the DJ segments 1-5 times and 29% listened >10 times. Overall the manual was used less than the songs; 12.5% reported not using the manual at all; 37.5% used it 1-5 times; only 23% used it >10 times in the prior 3 months. Participants rated each song and manual section on a 0 (hated it) to 10 (loved it) scale. Every song and all but one manual section received mean ratings over 8.5. The lowest mean song rating was for It Ain’t Easy at 8.6 and the highest mean ratings were That’s My Motivation and You Can Work it Out, both at 9. The lowest rated manual sections were Stress and Depression at 7.71 and Symptoms and Side Effects and Disclosure, both at 8.54. The highest rated manual sections were Your Support Team (9.37), Adjusting to Taking ART Medications (9.18), and Goal Setting (9.16). Regarding the 800 number, 47% reported not using it, probably because the clinic was easily accessible and patients preferred to come in or call the study office with questions. Overall, only a few participants made suggestions for changes to the LN. One person wanted more jazz, 2 wanted more songs, 1 said the music style was too young, and 3 felt the manual was too large.

In order to determine feasibility for this project in rural settings, we conducted 2 focus groups in June 2011 at study sites in Athens (health department) and Macon (Rainbow Center), GA. The sample consisted of 26 participants (69% male) between ages of 25 to 59 (mean= 46), 58% AA, 42% W, and 8% Hispanic, all but one person were currently on ART. The majority had a high school education or GED (58%) and reported income below \$1500/month (85%). 12 people identified as heterosexual and 11 as homosexual/ gay. Twenty-two of the 26 participants owned a cell phone (one smart phone). After an introduction and discussion of favorite music and artists, all songs and 2 talk show segments were played for each group with discussion immediately after each. Participants were asked to complete a program evaluation survey and rate the songs between 0 (hated it) to 10 (loved it) after listening. Copies of the pared down manual (60 pages) were distributed for review during the session. The participants provided excellent feedback and suggestions for the program. They preferred upbeat lyrics and genres and were quick to criticize songs with ‘depressing’ lyrics (It Ain’t Easy). People felt that HIV is depressing and didn’t want to be reminded of that through the songs. Some felt a few songs were too long. Participants responded favorably to the talk segments on side effects and disclosure. They felt the suggestions and strategies were relevant and realistic. Disclosure especially, generated lots of discussion regarding personal experiences. The revised 60-page manual was well liked, however a few felt it needed simplification, and several wanted to take one home. Participants felt putting the material into a mobile app was creative and liked the potential for an interactive manual via the app. Many agreed the program would not divulge their status, and that they could listen with headphones in public areas; however several reported they would probably only listen at home. We also discussed smart phone usage. Most did not own smart phones. Responses were a resounding “yes,” regarding willingness to use a second study provided phone; one participant said 2 phones would make him “look important.” All wanted training in smart phone use. General themes that emerged were: stigma, rejection, and isolation; depression was also strong and emerged as the reason for wanting uplifting and upbeat songs

("...don't go with a funeral dirge..."; "I wouldn't want to listen to that while I'm depressed."). The program was perceived as targeting AA (which was the predominant population of the urban site where it was developed and tested). Suggestions for additional and diverse genres were: pop, rock, country. Participants from the Rainbow Center, a housing program for HIV infected substance users, suggested including content on substance use. Additional topic suggestions were: drug holidays and drug resistance, more information on HIV, and importance of support groups. 'Hope' was perceived as the overall message of LN and was something everyone enjoyed hearing. One person wrote: "Very exciting and educational.... You have made a difference in my life." Results from the written evaluation survey validated the discussions. Similar to the urban group, the song with lowest rating was It Ain't Easy (28% hated/disliked). 22 (56%) strongly agreed or agreed with item 37, 'I think the songs could help me to remember to take my medications as prescribed.' We found significant positive nonparametric correlations with that survey item (37) and the following items: songs were uplifting ($r=.6$; $p=.001$), I could relate to the characters in the songs ($r=.5$, $p=.01$), and songs were interesting ($r=.4$, $p=.05$). Reinforcing the need for uplifting songs, there was a negative correlation with that item and 'songs were depressing' ($r=-0.4$, $p=.04$). Six songs (see Table 1) also had significant correlations with item 37. With respect to smart phone use, 24 persons reported they would be willing to carry a second phone (2 said maybe) if it were provided free of charge. All but one person reported being willing to learn new cell phone technology.

We have demonstrated success at developing and testing the LN and interest from both urban and rural PLWHA. Those urban participants receiving LN improved self-efficacy, exhibited a trend toward higher PC, a greater proportion had therapeutic drug levels in the acceptable range, and undetectable viral loads after 12 weeks of the study. The pilot urban participants had access to multiple clinic-based resources in a very comprehensive HIV treatment facility and we were able to demonstrate promising preliminary results when compared to standard care. We believe the LN shows promise for improving ART adherence and self-efficacy for adherence. We especially feel the value of our self-management program will be greater in areas with fewer resources, and where access to care may be limited. Our findings from the rural focus groups reinforce this need and support the mobile app and smart phone delivery and offer positive suggestions for culturally appropriate program revisions.

c. Significance

c.1 HIV/AIDS in rural areas Though most persons with AIDS in the US reside in large metropolitan areas, in 2007 about 8.3% resided in nonmetropolitan areas (defined as <50,000). The South contains the largest number of rural dwellers with AIDS,¹ and Georgia was 6th overall in the US for AIDS diagnoses per 100,000 in 2008.² In 2007, Georgia ranked second in reported cases of HIV among adults and adolescents in rural areas^{1,2} and in 2009 33% of PLWHA lived outside the 20 county metropolitan Atlanta area, where rural counties predominate.³ Georgia also has significant racial disparities in HIV/AIDS: African Americans represent 30% of the state's population, but 74% of its HIV/AIDS cases.³ Adding to the burden of rural HIV is evidence that individuals often migrate from urban centers (where they are typically diagnosed) to rural areas within the Southeast for family support.⁴ This strains the pool of federally allocated funding for HIV medical care and disproportionately redirects resources from rural regions back to urban centers.⁵

c.2 HIV/AIDS and adherence in rural areas: ART has transformed HIV/AIDS to a treatable chronic condition; however, patients are expected to maintain high levels of ART adherence to achieve sustained virologic suppression and immune restoration, and to avoid the sequelae of virologic failure.⁶ Such demand for high-level adherence has been a major constraint on the gains of ART; close to 50% of individuals experience treatment failure within the first year of initiating a new regimen.⁷ This is of particular concern in small town settings where HIV diagnosis is dogged by stigmatization and confidentiality concerns, and patients feeling the need to conceal HIV medications. Though sparse,

available data suggest adherence rates are suboptimal among rural PLWHA compared to their urban counterparts. Studies report 34%-50% of rural participants admitted missing one or more doses of ART in the past 7 days^{8,9} and 59% of rural women in the Southeast reported missing doses in the past month.¹⁰ These rates of missed ART doses are not inconsequential and contrast with higher rates of 71-78% we found in our Music Project pilot study in an urban cohort and rates of 80-90% reported by others.^{11,12} Interestingly, reasons identified for poor adherence in these studies were similar for both urban and rural dwellers, and they include factors such as ART side effects,^{4,13} an issue our program is designed to address. Other factors associated with poorer adherence among rural dwellers are non-white race, HIV non-AIDS, moving to rural area after diagnosis,¹³ problem drinking,¹⁴ avoidance coping, and women with children.⁵ Particularly among minority individuals in the Southeast, barriers to adherence included extra planning for medication taking, denial, life stress, shame and stigma, and ART regimen complexity. Adherence facilitators included factors such as acceptance, clear understanding of the consequences of non-adherence, spirituality and prayer, simplified ART regimens, and social support.⁵ Similar facilitators were identified in women in the rural Southeast.¹⁰ In another study, spirituality played an important role in treatment, especially among African Americans.¹⁵ Depression, a well-documented barrier to adherence, and psychological distress are noted to be higher in rural HIV infected persons compared to urban counterparts.^{16,17} Depressed patients report lower satisfaction with life, poor perception of social support as well as stressors like loneliness, stigma, and disclosure fears.¹⁷ Stress, depression, side effects, spirituality, and disclosure are all addressed in LN.

c.3 Adherence interventions in rural areas Presumably because of the challenges of working in these areas, only a few investigations have focused on adherence interventions in a rural setting. One pilot study which examined the feasibility of a motivational interviewing intervention among a rural clinic population reported high attrition rates and difficulty maintaining landline telephone contacts with participants.¹⁸ Suggestions were made to employ mobile phones – widely available to this population – to facilitate adequate patient follow-up, a strategy we adapt in this project. The RePORT database revealed only two NIH recently (2011) funded rural HIV adherence studies; an intervention using a text messaging system targeting HIV⁺ drug users (1R34DA031640-01, Ingersoll, K.) and a nurse delivered cell phone intervention targeting both urban and rural HIV⁺ persons (1R01NR012962-01, Kalichman, S.). This paucity of research demonstrates a significant gap and highlights the importance of our proposed project. The use of mobile technology in both underscores its suitability for rural areas. Our use of mobile apps, texting, and smart phones further exploits technology in this setting.

c.4 Music enhances recall and learning Music has universal appeal and the potential to evoke transformational learning in adults.¹⁹ Music-based messaging can enhance learning, retention, and recall of information.²⁰ Music provides a medium for disseminating messages in a culturally relevant manner that does not rely on literacy level and helps motivate individuals to initiate and maintain health behaviors through sounds and lyrics. Music-based messaging has been used effectively to promote sunscreen use,²¹ use of stairs,²² facilitate positive behaviors in patients with dementia,²³ reduce anxiety in chemotherapy patients,²⁴ enhance end of life care,²⁵ reduce stress, increase fiber, lower cholesterol intake and enhance one's perspective on life,²⁶ and reduce pain in elders with chronic osteoarthritis.²⁷ It has also been used in HIV prevention with several populations: teens,²⁸ rural residents in Ghana,²⁹ and by co-investigator Dr. Ofotokun, in rural African communities.³⁰ In our LN program we provide information, create experiences, and use verbal persuasion and motivation to strengthen self-efficacy for adherence through music and lyrics.

c.5 Potential impact The challenge for HIV+ persons is to achieve and maintain high levels of adherence to medications, some of which have rigorous dosing schedules and burdensome side effects, amidst the barriers encountered living in a rural area. The challenge for health care professionals, then, is to provide consistent and easy access to a high level of education and motivational support to PLWHA in rural areas where resources are limited and barriers such as stigma, travel distance, transportation,

and shortages of trained health care providers may preclude regular in-person visits with clinical staff for ART education and follow-up. We will use widely available smart phone and mobile app technology to test a practical adherence strategy that could potentially sustain the long-term benefit of ART among PLWHA in rural Georgia by improving self-efficacy for ART adherence. Should the LN app show promising results, this strategy, unlike many others that have been previously evaluated, could be rapidly scaled up to address the needs of rural populations nationwide. It can be easily incorporated into routine clinical ART adherence counseling. Because it is self-administered, training can occur during a routine clinic visit or at home. There is no visible identifying or stigmatizing characteristics. PLWHA in rural areas who use this program can blend in easily anywhere that portable playing devices and cell phones are used without fear of loss of confidentiality. Equipment that is increasingly ubiquitous (a smart phone with mobile apps) enhances the sustainability and as new information becomes available, updates can easily be downloaded to the app. With its focus on technology, the project helps bring rural health care into the 21st century³¹ and also exposes rural PLWHA to mobile technology; something they clearly desire. The development of self-management programs into a mobile app could also be adapted to improve adherence in other aspects of HIV-disease management. The potential impact of this project is major, and could transform the delivery of self-management and adherence education.

c.6 mHealth app use Approximately 90% of Americans own mobile phones, 58% of which are smartphones.³² Among those who used smartphones in 2013, 95 million accessed mobile health information, one of the fastest growing content categories among wireless users.³³ Thus, the ubiquity of mobile technology and growing public interest in health-related content make mobile health (mHealth) a desirable platform upon which to develop interventions aligned with national health care objectives: widening patient outreach, reducing costs, and improving long-term outcomes.³⁴ Despite the popularity of mHealth content, only 19% of wireless users reported having integrated mHealth apps into their daily routines.³⁵ Reasons behind this disparity are not well explained in the literature. Few studies have focused on theory-based factors affecting the acceptance and sustained use of mHealth interventions. Moreover, the contributions of individuals' technology associated characteristics (i.e., eHealth literacy and personal smartphone experience) to mHealth app usage have not been investigated. Venkatesh et al.³⁶ conceptualized consumer-oriented technology acceptance as a multidimensional construct in which behavioral intent, the main influence of action, forms the centerpiece. Within that framework, core interpersonal factors (performance expectancy, effort expectancy, hedonic motivation) act as antecedents to behavioral intent. In a non-medical study, these relationships accounted for 74% of the variance explained for behavioral intention and 52% for technology use.³⁶ This study seeks to evaluate the effect of these constructs on behavioral intent/usage of the LN/EP apps with the goal of refining and improving the sustainability of the mHealth intervention for future use.

2. Design

a. Sample

a.1 Population: For both parts of the study we will require a total of 250 PLHA in rural Georgia cities of Athens, Macon, Augusta, Brunswick, Columbus, Newnan, Americus, Oglethorpe, Cordele and Cuthbert . Age is adults age 18 and over.

a.2. Inclusion/exclusion criteria:

Focus Group volunteers: Inclusion criteria are: 1) HIV infection; 2) on ART; 3) ≥18 years of age; 4) English speaking; 5) willing to listen to the LN and use the mobile app and participate in a focus group to discuss opinions about the program and mobile app. Exclusion criteria are: history of or self-reported bilateral hearing loss, cognitive impairment.

RCT: Inclusion criteria for the study are: 1) HIV infection; 2) initiating ART for the first time (except women who may have had ART during pregnancy) or changing ART regimen within the past 3 months due to side effects or virologic resistance; or 3) HIV+ individuals with a detectable viral load \geq 40copies/ml; 4) HIV+ individuals on ART medication 5) \geq 18 years of age; 6) English speaking; and 7) willing to complete 4 assessments, monthly unannounced pill counts, and collection of hair samples, be randomly assigned to either condition, and participate in study activities that include using smart phone and mobile app. Persons will be excluded from the study if they are not HIV infected, homeless, are a minor under 18 years of age and therefore unable to give independent informed consent, are unable to read or understand English since all of the questionnaires and the audio program and manual will be in English, have a history of or self-report bilateral hearing loss, cognitive impairment (inability to comprehend the informed consent document), are actively psychotic, severely depressed/suicidal, or pose a risk of harm to themselves or others (Brief Symptom Inventory; BSI), since these persons may not be capable of using the mobile app or completing the assessments. Depending on the severity, these persons will be walked to or referred to the mental health counselor, once the mental health issues have been addressed, they may be re-screened for eligibility. Substance users will not be excluded from the study, except if they display the above mentioned mental health characteristics or pose a risk of harm to themselves or others.

b. Setting

The study sites are within 5 health district sites that provide care to HIV+ persons in rural counties in Georgia outside the 20-county Metropolitan Atlanta Statistical area (MSA). The sites of the project are:

District 5-2 North Central (Macon) is located in the central portion of the state. In 2012, there were 2802 persons living with HIV/AIDS in this district. The Hope Center provides the bulk of HIV care to persons living in the 13 counties that comprise District 5-2. The clinic offers a broad array of HIV health services: primary care, HIV maintenance care, pharmacy, laboratory, vision, and dental. Case management, nutritional counseling, community support, and mental health services are also available. From January 1 to Aug 2, 2011, the clinic reported a caseload of 776 clients. 61.5% of these individuals were male; 82% were African Americans; and 74% lived at or below the federal poverty level. Currently there are 647 persons on ART, about 150 people were started on ART, and 100 changed existing medication regimens in the previous year.

District 6 East Central (Augusta) is located in the east central portion of the state. In 2009 there were 2540 persons living with HIV/AIDS in the district. The only site for HIV care in this area is at the Georgia Health Sciences University. The infectious disease clinic serves persons from the 13 counties in District 6 as well as two South Carolina counties (Aiken and Edgefield). 11 of the Georgia counties and Edgefield County, SC, have less than 35,000 people, meeting the US Census Bureau definition of 'rural'. 10 Georgia counties are designated as Medically Underserved Areas (MUA), three are designated as having Medically Underserved Populations (MUP); and 12 meet the criteria for Primary Health Professional Shortage Areas (HPSA's). The infectious disease clinic has 1314 patients and about 70% are African American and 71% are at or below the federal poverty level. The clinic provides comprehensive primary care to HIV infected persons including pharmaceutical assistance, nutrition services, mental health and substance abuse services, and dental services. There are about 12 new patients a month, and 83% of all patients are on ART.

District 9-1 Coastal (Brunswick) is located on the southeastern coast of Georgia. There are five HIV care clinics serving people in 12 counties. In 2009 there were 2829 persons living with HIV/AIDS in the district, the largest outside the 20-county metropolitan Atlanta area. Ten counties are rural; seven of the counties are designated MUA and seven are HPSA. The clinics serve about 1100 clients, 75% of

whom are African American, 40% are women, and 75% are living below the federal poverty level. There are about 166 new clients a year and about 12 starting new ART regimens per month.

District 10 Northeast (Athens) is located in the northeast part of Georgia and contains ten counties, six of which meet the criteria for rural and nine of which are MUA. Eight are HPSA. The Specialty Care Clinic in Athens provides comprehensive primary care services, nutritional assessment and education, mental health and substance abuse care and referrals for specialty care such as dental and obstetrics. Other services include case management and transportation assistance. In 2010, the Specialty Care Clinic served 401 HIV infected adults, of whom 57% are African American, and 72% live at or below the federal poverty level. From January 1 through July 31, 2011 there were 35 new patients, and 50% of these were naïve to ART and began ART and about 5-8 patients change ART medications each month.

District 7 West Central (Columbus) is located on the west border of central Georgia. This health district is comprised of 16 counties. In 2012 this district had a rate HIV/AIDS of 1,855 per 100,000 population. 15 counties are rural; 14 of the counties are designated MUA and 16 counties are HPSA. The clinics serve about 704 clients, 72% of whom are African American, 36% are women, and 72% are living below the federal poverty level. There are about 34 new clients a year and about 6% of the clinic population is starting new ART regimens per month. Also has satellite clinics in Americus, Oglethorpe, Cordele and Cuthbert.

AID Atlanta's Haven of Hope is located in Newnan, Georgia. HIV primary care services offered by acquiring Ryan White Part B & C funding to serve HIV+ residents in Public Health District Four (4) which was formerly administered by the District 4 Public Health division. This clinic serves 12 counties.

Ultracare Medical Office is located in Columbus, Georgia. The medical practice specializes in Infectious Disease and Internal Medicine.

All clinics are in the Georgia Public Health System, receive Ryan White funds, have access to the AIDS Drug Assistance Program (ADAP), and provide HIV care and medications. According to 2009 data the Coastal District in Savannah has the highest number of PLWHA (2829) outside the Atlanta MSA and is Georgia's third largest Ryan White provider. It is followed by the East Central District in Augusta (2540). Other sites are the North Central District in Macon (2286), and Northeast District in Athens (811) and Columbus (1388). These agencies cover the northeastern, southeastern, and central parts of Georgia and represent 54 (34%) of the state's 159 counties. Of the 54 counties represented in these districts, 40 (74%) have a population of <35,000; 52 (96%) were designated as medically underserved areas (MUA) or populations (MUP); and 47 (87%) were designated as Health Professional Shortage Areas (HPSA's) by the US Health Resources & Services Administration in 2009. The clinics serve a vulnerable group. Each clinic serves a majority of African Americans who are at or below the poverty level. We will be hiring a local study site coordinator who will be trained by the project coordinator to conduct all study activities at each site. This will ensure culturally appropriate research site coordinators who understand the people and locale. It will also eliminate any burden on the site staff.

c. Recruitment

c.1 Site: Participants will be recruited from each site by the local study site coordinator.

c.2 Methods: Posters and fliers will be posted at each study site and given to site staff for distribution. Potential participants will be referred by providers, case managers, nurses at the sites and may also self refer. Potential participants will receive written materials about the study and will be

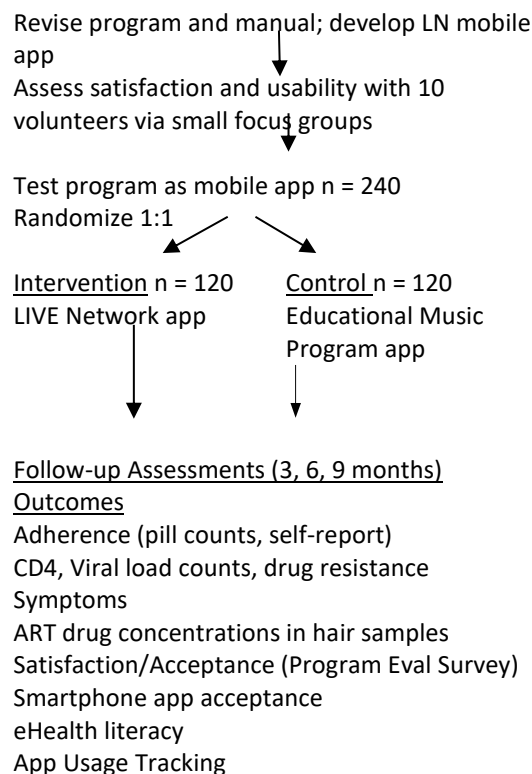
asked if interested. Study staff will be trained to deliver a presentation briefly explaining the study and answering questions about the study.

c.3 Materials: These are to be developed and will be forwarded when completed.

c.4 Monitoring: Our goal is to recruit a total of 10 persons for the focus groups (3-5 from 2-3 sites) and 240 for the main study. For the main study, our goal is about 10 persons per month (from all sites). We will assess recruitment progress monthly. If recruitment falls short we will add additional sites. If we remain behind we will expand eligibility criteria to include all persons on ART.

d. Procedures

d.1 Study design



d.2 Procedures for subjects

d.2.1 Data collection procedures:

Focus groups. Once all apps are completed, we will ask 10 volunteer rural PLWHA who are on ART (3-5 from each of 2-3 sites) to provide feedback using a small focus group format. We will demonstrate use of the phone and app and observe participants use all aspects of the app: LN music program, interactive manual, pill count. Participants will be asked to share their opinions about them in small group format. Questions will include user-friendliness, acceptability, understandability of content and method of presentation, and suggestions for improvement. Participants will also complete a Program Evaluation Survey that contains questions about likeability, favorite songs, ease of use, suggestions for improvement. Focus group sessions will be audio recorded with the permission of participants for the purposes of data collection.

RCT: Sources of information will include baseline, 3, 6, and 9- month follow-up assessments and tracking of usage of mobile app conducted solely for the purpose of this research. Assessments will include assessments of adherence to antiretroviral medications and, measures of symptoms, depression, self-efficacy, attitudes, goals, demographic information including substance use, and health literacy. Physiologic measures will include ART drug levels in a small hair sample (100 strands) cut from the occiput (back of head) at each time point. Lab results for CD4, viral load, and drug resistance will be extracted from medical records consistent with the study time points. Study assessments will be conducted in person using ACASI coincident with provider appointments. They will last about 3 hours. Monthly unannounced pill counts will be conducted via smart phone using the camera and pill count survey within app with assistance from the clinical research coordinator as needed. As part of our reliability testing, up to 60 participants will be asked to repeat their pill count about 24 hours after baseline. Hair samples will be collected in person by study personnel on-site at each time point. Tracking usage of the app will be done via the mobile web application which will send messages to the HIPAA compliant server each time a participant uses the app. Participants will be assigned to one of two conditions: an educational music program (EP) or the LN treatment condition. All participants will receive the usual care at their respective HIV care agencies. Evaluation information will be obtained about the satisfaction and use of the programs at the end of the RCT study. The option of 3, 6, and 9 month follow up study assessments administered via phone call will be offered to participants who are unable to complete in person visits. If this option is elected the hair sample and visual analog scale data will not be collected.

d.1.b Other interactions

Participants will receive reminder calls and text messages regarding study appointments. Text messages will also remind them to listen to the LN & EP.

d.2 Respondent burden

For the **Focus group** respondent burden will be participation in a 3 to 3.5 hour group where they will view and return demonstration of use of the smart phone and LN mobile app and provide feedback both written and verbal. For the **RCT** participants will be in the study about 10 months, and will be asked to listen to and use the LN mobile app during that time. They participate in 4 computer interviews that are around 3 hours each, and provide 100 strands of hair at each interview. They will also participate in monthly unannounced pill counts via mobile app or telephone call.

e. Measures

Behavioral measures will include: 1) assessments of adherence to antiretroviral medications; 2) measures of symptoms, depression, self-efficacy, attitudes, goals, demographic information including substance use, and health literacy; and 3) smartphone app acceptance and usage measures, along with eHealth literacy and smartphone experience. Physiologic measures will include ART drug levels in a small hair sample (100 strands) cut from the occiput (back of head) at each time point. Lab results for CD4, viral load, and drug resistance will be extracted from medical records consistent with the study time points. Usage tracking will be captured via the previously mentioned mobile web application, which will transmit messages to the HIPAA compliant server each time a participant uses the app. A table with a list of measures and copies of each instrument is uploaded into the IRB application.

f. Risks to participation

f.1 For **Focus groups** there is a risk of breach of confidentiality when persons come together in a group format. The risks include identification/disclosure as HIV+ to others in the group and discussion of

private information outside the group. There is a remote risk of anxiety or stress related to the discussion content. For the **RCT** there is a very remote risk of injury from clipping hair samples. Completion of the assessments and participation in the interventions are free of risks for physical harm. However, both the assessments and the intervention may raise personal issues, which may be troublesome to some of the participants. Some participants may feel anxious as a result of dealing with these issues. Use of the mobile app and text messaging could display private information. These risks will be explained in the consent form. All study staff will be trained in the mental health aspects of HIV/AIDS, how to recognize and deal with emotional or behavioral problems, including anxiety, as they arise, and will be asked to report all adverse events to the principal investigator.

f.2 Procedures to reduce Risk

f.2.a. Recruitment and Consent Procedures

Men and women who meet the study criteria will be recruited at the HIV Clinics described above. Site coordinators will be trained to deliver a presentation briefly explaining the study and answering questions about the study. Potential participants will receive written materials about the study and will be given a phone number to call. Individuals who are interested in participating will be given a screening assessment to assess eligibility. Before the screening assessment, the study will be explained in detail including the purpose of the study, the participant's role in the study, study requirements, and time commitments, confidentiality and privacy protections (including for focus groups and RCT), and questions will be answered. Potential participants will be assured that their care at the clinic will not be affected in any way by their decision whether or not to participate in the study. They will be given an opportunity to ask questions and receive additional explanation. The consent form includes an explanation of the study, the risks and benefits of participation, the duration and type of participation, description of the procedures, contact person for the research including the chair of the IRB, the voluntary nature of participation, and the right to withdraw without penalty will be read and explained. Since this population is at risk for cognitive impairment that, in some cases, may limit capacity to provide consent, a consent post-test will be administered to evaluate understanding of study procedures, risk/benefits, etc. If this is completed with 100% accuracy, they will be asked to sign an informed consent form, and given a copy of the form for their records. For focus groups, the group will begin thereafter. For the RCT, they will next complete the BSI screening and if the results of the screening assessment indicate that they are eligible for the study, they will be given an invitation to participate. They will then begin the baseline assessment.

f.2.b. Protections Against Risks

To minimize the risks associated with clipping hair, we will train and check off each site coordinator, and establish reliability between and within coordinators in their ability to follow established protocols consistently. In addition to the above procedures regarding possible mental health risks, using a coding system for tracking assessments will minimize threats to confidentiality. All confidential information including code numbers and data will be kept in a locked office in locked file cabinets with limited access. Names will never be linked with data. All study data will be kept on a secure password protected, HIPAA-compliant server at Emory University. Flash videos associated with the music program will not display terms such as HIV/AIDS that could disclose status. We will encourage use of the interactive manual, which will contain specific HIV related information, in a private area. Any text messages sent will not contain private information or terms that may disclose status. Code words will be used when needed to send reminders to use the app, and for assessments, pill counts. When calling participants, we will always ask if they can talk privately and if not, set a time to call back. The project name "Music for Health Project" does not contain terms that could be associated with HIV/AIDS. LN and EP usage data will be tracked on a HIPAA-compliant secure server at Emory University.

To ensure that information discussed in all focus group sessions is kept confidential, a reminder contract will be read at the beginning of every session. This verbal contract will emphasize that each participant is responsible, as are the staff, for not discussing information outside of the room and not disclosing participant names or identities to others outside the room. Only first names will be used in all focus groups. Digital audio recordings used for data collection for focus groups will be labeled by a group number and date. These will be kept in on a secure server with limited password protected access. The transcriptionist will follow a strict check out and confidentiality procedure for transcribing recordings; no names/identifiers will be used when transcribing, analyzing, or reporting the data. In addition to the above procedures regarding the slight possibility of emotional response or anxiety, all our staff are trained to provide emotional support to anxious or stressed out participants. We have an established protocol for mental health referrals and there is an existing mental health referral system at each site, which we will use if needed. Participants will be informed they may stop participation if it is stressful to them.

In order to main confidentiality, all study staff and site coordinators will be required to sign a confidentiality statement.

g. Benefits to subject or future benefits

The benefits of our intervention include learning about antiretroviral medications, ways to enhance adherence, ways to problem solve and develop personal strategies for taking ART consistently, ways to self-manage symptoms, and receipt of the incentives to promote retention in the project. We believe that the benefits of the intervention outweigh the possible negative consequences.

h. Data analysis

h.1 Rationale for proposed number of subjects and sample calculations

The target sample size is 200 participants with 100 allocated to each group. Taking into account projected attrition of about 40 persons, we expect a final sample size of 240. Given our approach using multi-level longitudinal models (MLM) for these 200 subjects, 2 groups at 4 time points, we are 95% confident that power levels between 84% to 98% will achieve minimal detectable differences of 0.4 (within time and group by time) and 0.5 (between groups) (small-to-moderate effect sizes) for random effects subjects variance equal to 1. Covariate adjustments should further reduce variability and detectable effect sizes while increasing power. Additionally, to address the differences in proportion achieving virologic suppression and drug resistance, a chi-square test for a sample size of 200 yields a small-to moderate effect size (W) of 0.1981 for 1 degree of freedom (2 x 2 table) at 80% power and 5% level of significance.

h.2 Plans for data management and analysis

h.2.a Data management Procedures for data management and monitoring will be initiated during the start-up phase. The project coordinator will coordinate the organization and processing of forms, and schedule and implement checks of data quality and completeness. Data from the ACASI files will be saved in the QDS data warehouse. Data will be backed up on a regular basis to prevent loss of data. Data will be transferred electronically from the sites to a secure password protected, HIPAA-compliant server at Emory University. A data-checking plan based on each questionnaire will be used to look for suspicious entries. Data monitoring will include scheduled checks for completeness every 2-4 weeks. Data sets from all assessment points will be merged as necessary to answer the research questions. Personal goals will be reported by the participant and typed into the database for qualitative analysis. They will be analyzed for the dimensions of content, specificity, effectiveness, and control. Dr. Higgins will oversee the final quality assurance/quality control data reviews. She will design and conduct the statistical analyses; assist as with designing research forms and data entry; and collaborate with the

investigators on analysis and interpretation. We have successfully used these procedures with the pilot project and other research projects.

h.2.b Analysis Initial analysis will include descriptive statistics of sample characteristics (demographics, substance use, depression scores, etc. and CD4 and Viral Load.) and psychometric evaluation of all scored instruments. A combination of statistical software will be used for statistical analysis and data visualization, including SPSS (v.19), SAS (v. 9.2), and R (v. 2.13). Distributions, potential outliers, and patterns of missing data will be assessed to assure that the data meet assumptions for subsequent inferential tests. Missing data imputation methods may be used for small amounts (<5%) of missing data such that missing data are random. All statistical tests will be performed at the 5% level of significance, with exact p-values reported. Intent-to-treat procedures will be employed. For non-normal data, transformations may be performed to improve deviations from normality. However, it is well known that PC, viral loads and adherence measures are often skewed and experience floor and/or ceiling effects. Therefore, generalized linear models (GLM)/generalized estimating equations (GEE) frameworks will be employed as a more accurate reflection of the true underlying distributions generating these data. It is expected that logistic (logit)³⁷ and log-gamma³⁸ may be appropriate as well as Poisson, zero-inflated Poisson, and other link functions.^{39, 40} Additionally, it is expected that some attrition over time will occur. Mixed/multi-level models (MLM) will be used instead of repeated measures analysis of variance (RM-ANOVA) methods since MLM uses all available data (does not delete cases with missing values over time), handles data that are missing at random (MAR) which RM-ANOVA cannot, does not assume independence across time, provides a breakdown of variance both within and between subjects, and allows for both time-invariant and time-varying covariates.^{39, 40} It is expected that the majority of the analyses will occur in SPSS. However additional MLM and GLM/GEE models will be run using SAS (PROC MIXED, PROC NLMIXED) and R (packages: LME4, GAMLSS as well as BRugs, which employs Bayesian estimation methods.⁴¹⁻⁴³

Satisfaction (Aim 1) Two assessments will be conducted and analyzed to determine participant satisfaction with the mobile app in general, LN program and interactive manual. Both times, we will ask questions about likeability, usage rates, ease of use, acceptability, satisfaction, relevance, favorite song, understandability, and suggestions for improvement. The first assessment will entail observations and discussions with rural PLWHA while using the mobile app in focus group format. Observations and discussions will be recorded and content analyzed for themes, which will inform final revisions to the LN app. The second feasibility analysis will be the Program Evaluation Survey at the end of the study. Scaled responses to questions related to the above criteria will be analyzed using descriptive statistics and written comments will be entered into nVivo software and content analyzed for themes. We will also describe and evaluate the usage data from the web application designed to track app usage. We will determine average usage patterns and compare between groups (LN vs. EP).

Outcomes (Aim 2) All covariates will be evaluated to determine if any differences exist at baseline between the 2 groups (LN and EP), as well as testing for interactions (moderation) between groups and time. Inter-correlation among the covariates will also be evaluated. Multicollinearity diagnostics (variance inflation factors, tolerance, condition index) will be used to determine which covariates should remain in the subsequent models. MLM longitudinal models as detailed above will be used for each outcome (H1: adherence, H2: drug levels, and H3: CD4, viral load, drug resistance) to test differences between the 2 groups (group main effect), test for changes/differences from baseline to 3, 6 and 9 month (time main effect) and test for group by time effects (i.e. changes from baseline that are differences between the 2 groups) adjusting for significant covariates/moderators as needed. Appropriate link functions (e.g. logit, Poisson, other) will be assessed for each outcome within the MLM.

Exploratory outcome, mediators and moderators (Aim 3) Symptoms and symptom management scores will be examined using MLM as described above. Self-efficacy, outcome expectancy and personal goals are mediators in our model and meet the criteria for mediators as defined by Baron and Kenny⁴⁴

and Bennett.⁴⁵ First, the intervention is designed to foster change in self-efficacy, outcome expectancy, and personal goals, and second, the mediators, in turn, are associated with the outcomes of adherence and symptoms. A number of authors have explicated the process by which mediation can be tested.^{46, 47} A combination of statistical methods will be employed to determine the significance of mediation effects through the SPSS macro as described in Preacher and Hayes.⁴⁸ This SPSS macro runs the Baron and Kenny method and Sobel⁴⁷ test, as well as a non-parametric bootstrapping estimate, which is a more rigorous alternative to the Sobel test of the indirect effects. Based on the outcomes of these tests, each potential mediator will be assessed as to whether it provides for total, partial, or no mediation effect. Moderators such as depression and health literacy will be tested for main effects (differences at baseline) as well as for interaction (moderation effect) with the intervention (group) and across time. These moderation effects will be included within all mediation models to assess the extent of mediation of self-efficacy and outcome expectancy on adherence outcomes after adjusting for moderators and covariates.

Smartphone acceptance (Aim 4) Multivariate regression models will be used to address each hypothesis related to this aim. For Hypothesis 1, each antecedent (effort expectancy, performance expectancy and hedonic motivation) will be tested as a significant predictor of behavioral intent after adjusting for potential demographic covariates, such as age and gender. For Hypothesis 2, a simple regression model will assess the amount of association between behavioral intent and LN/EP app usage. For Hypothesis 3, multivariate regression will again be used to test for the moderating effects (i.e. two-way interaction effects) of smartphone experience and eHealth literacy on the association between the antecedents and behavioral intent. In place of traditional regression methods, the PROCESS plug-in macro for SPSS⁴⁹ will be employed using methods outlined by Hayes⁵⁰ to test the moderation effects of both smartphone experience and eHealth literacy on behavioral intention. (Note: for a continuous predictor variable and a continuous moderator variable, each will be mean-centered using the PROCESS macro before computing the interaction variable to avoid mathematically induced multicollinearity issues present for moderation testing.)

Exploratory outcome (Aim 5) Analysis includes the first 106 participants in the main study and participants are compared based on their inclusion criteria (participants switching ART medications because of new resistance (non-adherence) vs those starting or switching ART medication for non resistance reasons or toxicity). Data will be de-identified by the Rural Music Project data manager prior to analysis. The data manager will not conduct any data analysis for this aim. Baseline ACASI data will be merged with inclusion criteria data from site tracking log based on the participant identification number and analyzed using SAS (v. 9.4) statistical software.

3. Training research personnel

Interviewer training Experienced interviewers will be trained to conduct baseline and follow-up interviews. To control for measurement error, we will be using ACASI to administer most of the items. Interviewers will also be trained in hair sample collection, processing, and storage. This process will be standardized based on the equipment and procedures. We will develop procedures manual which includes all the important elements of interviewing along with specific information related to each item on the questionnaires/surveys, as well as written procedures for hair sample collection, processing, and storage. This manual will serve as the basis for training. Interviewers will use standardized scripts to introduce the participant to the study and explain the questionnaires/surveys, and procedures. The interviewers will practice the survey, screening, baseline, and follow-up scripts with each other. They will practice hair-sampling procedures on models. Weekly meetings and contact with the PI will be held to discuss problems and issues that may arise.

Focus group facilitator training Two focus group facilitators will conduct the groups. They will be trained in group dynamics and how to ask general questions and more specific questions. They will use a script written by the PI and Co-I to elicit comments about the LN app and smart phone use.

4. Plans for data management and monitoring

As mentioned above the potential risks from this study are minimal and we had no adverse events during the pilot study of the Music Project (n = 77). Therefore, adverse events and clinical outcomes will be monitored by the Principal Investigator (PI) in collaboration with the Co-Investigators (Co-I's). All study staff will be trained to recognize and report adverse events immediately to the PI who will report them to the Emory University IRB. Data management will be done by the study project coordinator who will assure quality and security of the data from start through conclusion of the project and will notify the PI of any breaches in data security. S/He will also provide real-time checks of forms-based data, and at least monthly monitoring of data quality and completeness.

The PI will review the following indicators on a monthly basis.

- a. adherence to the goals for recruitment and retention;
- b. adherence to the study protocols;
- c. cumulative data for evidence of study related adverse events;
- d. quality, accuracy, completeness, and timeliness of the data collected thus far;
- e. factors that could affect the outcome or compromise participant/data confidentiality;
- f. other factors outside the study (e.g., therapeutic developments, agency related policies) that could impact the safety of participants or the ethical conduct of the study.

In general, if problems arise, the PI will consult with Co-I's and the IRB to make possible recommendations:

- a. continue the study without change;
- b. modifications to the study protocol;
- c. suspension or early termination;
- d. alternative approaches to consider (e.g., if there is a failure to accrue participants as anticipated, such as addition of another site).

If a breach in data or individual confidentiality, a study related adverse event, or a significant protocol violation occurs, the PI will contact the IRB as soon as possible to discuss and make recommendations for action.

5. Confidentiality

See 'f' above.

6. Informed consent

The informed consent for each part of the study has been downloaded to the e-IRB application.

Individuals who are interested in participating will be given a screening assessment to assess eligibility. Before the screening assessment, the study will be explained in detail including the purpose of the study, the participant's role in the study, study requirements, and time commitments (including for the intervention and assessments), and questions will be answered. Potential participants will be assured that their care at the agency will not be affected in any way by their decision whether or not to participate in the study. They will be given an opportunity to ask questions and receive additional explanation before signing the appropriate consent form which includes an explanation of the study, the risks and benefits of participation, the duration and type of participation, description of the procedures,

contact person for the research including the chair of the IRB, the voluntary nature of participation, and the right to withdraw without penalty. If interested, they will be asked to sign an informed consent form and will be given a copy of the form for their records.

7. Plans to inform participants of new findings or research results that might affect health

The following statement has been added to the consent form for the main pilot study.

New Findings: If significant findings are found during this research, this information will be provided to you.

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